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(54) **Use of lower alkanoyl L-carnitines to produce a medicament suitable for the therapeutic treatment of retinopathies**

(57) The use of lower alkanoyl L-carnitines (e.g. acetyl L-carnitine) and the pharmacologically acceptable salts thereof to produce a medicament suitable for the therapeutic treatment of retinopathies, e.g. the age-related maculopathy (ARM) and non-age-related maculopathy (nARM), is disclosed.

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Description

The present invention relates to the use of lower alkanoyl L-carnitines and the pharmacologically acceptable salts thereof to produce a medicament suitable for the therapeutic treatment of retinopathies, particularly the age-related maculopathy (ARM) and non-age-related maculopathy (nARM) and for the prophylaxis and treatment of age-related macular degeneration (AMD). Further retinopathies that can be successfully heated according to the present invention include diabetic retinopathy, neuroretinopathies, e.g. the Batten-Mayou disease and the inherited dominant drusen.

By "lower" alkanoyl, any alkanoyl group having 2-6 carbon atoms is meant. Acetyl, propionyl, valeryl and isovaleryl are preferred alkanoyl groups. Acetyl is particularly preferred.

Previous ophthalmological applications of both acetyl L-carnitine and acetyl D-carnitine are already known.

US patent 5,037,851 describes the use of acetyl L-carnitine and its pharmacologically acceptable salts in the therapeutic treatment of cataract.

US patents 5,145,871 and 5,432,199 describe the use of acetyl D-carnitine and its pharmacologically acceptable salts in the therapeutic treatment of glaucoma.

There is no relationship between the above-mentioned diseases and age-related macular degeneration other than the self-evident fact, of no aetiological or therapeutic importance, that these are all diseases of the eye.

Cataract is the disease consisting in congenital or degenerative progressive opacification of the lens, i.e. of the biconvex, transparent lenticular structure of the eye located between the iris and the vitreous body.

Although the risk factors for cataract and, particularly, for AMD have not been clearly defined, it has been demonstrated that surgical removal of a cataract leads to progressive aggravation of any associated maculopathy (Liu et al., *Am. J. Public Health* 1989; 79: 765-769; Van der Schaft T. et al., *Br. J. Ophthalmology* 1994; 78: 441-445; Klein R. et al., *Arch. Ophthalmol.* 1994; 112: 191-196; Pollack A. et al., *Ophthalmology* 1996; 103: 1546-1554).

The term glaucoma refers to a group of eye diseases characterised by a progressive degeneration of optic nerve due to either vascular or mechanical pathogenesis, this latter consisting of an increased resistance to the outflow of aqueous humour via the trabecular reticulum at the level of the irido-corneal junction.

Age-related macular degeneration, on the other hand, is a disease belonging to the retinopathy group and specifically involving degeneration of the macula, one of the structures of the retina.

The macula is a yellowish ovoid zone measuring 2-5 mm in diameter located on the surface of the retina in line with the centre of the cornea. This zone is densely

packed with highly specialised photoreceptors, particularly cones, for the perception of light and is therefore regarded as the site of maximum acute and discriminatory visual capacity.

Degeneration of this area of the retina, as occurring in age-related macular degeneration (AMD), is an important cause of reduction and even of loss of vision in the elderly, particularly in industrialised Western countries and is therefore a disease with a substantial social and economic impact.

A recent epidemiological study (Br. J. Ophthalmol. 1996; 80: 9-14) has revealed, for instance, that in Great Britain alone 35,000 people are registered every year as totally or partially blind, and that more than 50% of these suffer from AMD. According to the Framingham Study (Surv. Ophthalmol. 1980; 24 (suppl.): 355-610), age-related macular degeneration may affect 20% of the population aged 65 and above as compared to less than 2% of the population aged from 52 to 64. The Beaver Dam Eye Study (Ophthalmology, 1992; 99: 933-943) has shown that approximately 35% of the population aged 75 and over are suffering from AMD.

This means that from 6 to 11% of the elderly population in the United States today are progressively limited in their social life as their vision deteriorates.

A European study (Acta Ophthalmologica Scandinavica, 1995, suppl. 217) reports an increase in the prevalence of age-related macular abnormalities from 14.6% in the 60- to 64-year-old age group to 45% in the 75- to 80-year-old age group.

The aetiology of the disease has yet to be thoroughly clarified, amongst other things because the studies on the causes of AMD have been limited by a shortage of suitable tissues from human donors and by the lack of a representative animal model.

The term AMD encompasses a broad range of morphological abnormalities which reflect the complexity of a disease which is probably of multifactorial aetiology with a complex interaction between genetic predisposition, ageing, environmental factors and life-style.

The disease is of a progressive nature.

ARM is a disease of the macular area of the retina which is mostly detected clinically after the age of 50 and is characterised by one or more of the following signs:

- presence of discontinuous yellowish-white excrescences or nodules (spots) called drusen which are external to the neuroretina or the retinal pigment epithelium. They may be soft and confluent (soft drusen), often with indistinct margins. Hard drusen, which are usually present in both retinas affected and not affected by ARM, are not in themselves signs of the disease;
- areas of increased pigmentation or hyperpigmentation associated with the drusen;

- areas of depigmentation or hypopigmentation of the retinal pigment epithelium without visible choroidal vessels associated with the drusen. The last stage of ARM is called age-related macular degeneration (AMD). AMD thus constitutes the ultimate evolution of ARM and includes both dry or atrophic AMD and wet or exudative AMD.

For a more detailed definition and international classification of ARM and AMD, see Survey of Ophthalmology 1995; 39: 367-374, a publication which is incorporated herein by reference.

To date, there is no valid therapy either for slowing down the aggravation of the macular degeneration or for reducing the high incidence of blindness as a complication of AMD, with the exception of parasurgery by laser photocoagulation in forms of neovascularisation of the choroid (i.e. of the membrane enveloping the retina) which are, however, the less frequent forms of degeneration. Therapeutic measures in ARM and AMD are currently limited, in practice, to alimentary supplementation for prophylactic purposes with vitamins, mineral salts and antioxidants. These treatments, however, present no proven efficacy. Particularly serious, moreover, is the fact that the macular degeneration is very often bilateral.

It will be appreciated, therefore, that there is a need for a medicament capable of slowing down and possibly arresting the progress of ARM, nARM and AMD.

The object of the present invention is therefore to provide such a medicament.

It has now been found that the aforesaid alkanoyl L-carnitines and particularly acetyl L-carnitine and its pharmacologically acceptable salts achieve the following objectives: therapy of age-related maculopathy (ARM), therapy of age-related macular degeneration (AMD) both in the dry and exudative forms, pharmacological therapy combined with surgery (laser photocoagulation for exudative forms of AMD), support therapy in ARM patients submitted to surgery for cataract in order to prevent ARM from developing into AMD, and therapy for non-age-related maculopathy (nARM) in patients aged under 50.

The object of the present invention is therefore the use of an alkanoyl L-carnitine (the term "alkanoyl" being as previously defined) or the pharmacologically acceptable salts thereof to produce a medicament suitable for the therapeutic treatment of age-related maculopathy (ARM) and non-age-related maculopathy (nARM) and for the prophylaxis and treatment of age-related macular degeneration (AMD), as well as for the treatment of the other retinopathies previously indicated.

It has also been found that, although the daily dose to be administered depends, according to the judgement of the primary care physician, on the subject's weight, age and general condition, it is generally advisable to administer from 1 to 4 g/day, and preferably 2 to 3 g/day of acetyl L-carnitine or an equimolar amount of

one of the other aforesaid alkanoyl L-carnitines or a pharmacologically acceptable salts thereof, even if larger doses can be administered in view of the substantial non-toxicity of acetyl L-carnitine and the other alkanoyl L-carnitines.

The medicament of the invention can be obtained by mixing the active ingredient (acetyl L-carnitine or one of the other alkanoyl L-carnitines or a pharmaceutically acceptable salts thereof) with appropriate excipients suitable for the formulation of compositions which lend themselves to enteral administration (particularly oral) or to parenteral administration (particularly intramuscular or intravenous). All such excipients are well known to experts in pharmacy and pharmaceutical technology.

What is meant by pharmacologically acceptable salts of an alkanoyl L-carnitine are any of its salts with an acid that do not give rise to unwanted side effects. Such acids are well known to pharmacologists and to experts in pharmacy and pharmaceutical technology.

Non limiting examples of such salts are chloride, bromide, orotate, acid aspartate, citric acid, acid phosphate, fumarate and acid fumarate, lactate, maleate and acid maleate, acid oxalate, acid sulphate, glucose phosphate, tartrate and acid tartrate.

A number of examples of formulations in the form of unitary doses are provided here below.

(a) Formulation for tablets

One tablet contains:

Active ingredient

- acetyl L-carnitine.HCl 590 mg
(corresponding to 500 mg of acetyl L-carnitine, inner salt)

Excipients

- microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate, cellulose acetate phthalate, diethylphthalate, dimethicone

(b) Formulation for intravenous injectable ampoules

One ampoule contains:

Active ingredient

- acetyl L-carnitine 500 mg

Excipients

- mannitol

One solvent ampoule contains:

- water for injections, q.s. up to 5 ml

(c) Formulation for sachets

One sachet contains:

Active ingredient

- acetyl L-carnitine.HCl 590 mg
(corresponding to 500 mg of acetyl L-carnitine, inner salt)

Excipients

- silica gel, sodium saccharine, hydroxypropyl-cellulose, sodium bicarbonate, tonic water (1 x 1000), mannitol.

(d) Formulation for extemporaneous solution

One 12.316 g vial contains:

Active ingredient

- acetyl L-carnitine.HCl 12.0 g
(corresponding to 10.17 g base)

Excipients

- methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, polyvinylpyrrolidone.

Whilst several clinical studies have been conducted, the results of a study wherein acetyl L-carnitine was used as active ingredient is summarised hereinbelow:

Fifteen patients aged from 40 to 85 years suffering from age-related maculopathy with drusen-type macular lesions were treated for 3 to 6 months with 2 g of acetyl L-carnitine daily *per os*.

At the end of the acetyl L-carnitine treatment, the following findings were detected:

- ocular fundus unchanged;
- no increase in number or development of drusen at fluorangiography;
- no deterioration of photopic visual acuity;
- no deterioration of contrast sensitivity;
- no deterioration of computerised threshold campimetry;
- no deterioration of electrofunctional test variables such as: visual evoked potentials, patterns at low, medium and high spatial frequencies; flash-type

visual potentials; photopic, scotopic and massive electroretinogram (ERG); threshold electro-retinogram (STR); oscillatory potentials.

Several patients also showed a marked improvement in a number of electrofunctional tests such as STR and massive ERG, and in the photopic visual acuity tests.

Absorption of the exudate associated with the drusen was also observed.

Claims

1. Use of an alkanoyl L-carnitine wherein the alkanoyl group has 2-6 carbon atoms or a pharmacologically acceptable salt thereof for producing a medicament for the therapeutic treatment of retinopathies.
2. The use of claim 1 wherein the alkanoyl L-carnitine is selected from the group comprising acetyl, propionyl, valeryl and isovaleryl L-carnitine.
3. The use of claim 1 or 2 wherein the medicament is for the therapeutic treatment of age-related maculopathy (ARM) and non-age-related maculopathy (nARM), diabetic retinopathy, neuro-retinopathies (Batten-Mayou disease and inherited dominant drusen) and for the prophylaxis and treatment of age-related macular degeneration (AMD).
4. The use of claim 1, wherein the medicament is an orally or parenterally administrable composition suitable for administering to a patient affected by age-related maculopathy (ARM), non-age-related maculopathy (nARM) and age related macular degeneration (AMD) 1-4, preferably 2-3 g/day, of acetyl L-carnitine or an equimolar amount of propionyl, valeryl or isovaleryl L-carnitine or a pharmacologically acceptable salt thereof.
5. The use of any of the preceding claims wherein the pharmacologically acceptable salt is selected from the group comprising chloride, bromide, orotate, acid aspartate, citric acid, acid phosphate, fumarate and acid fumarate, lactate, maleate and acid maleate, acid oxalate, acid sulphate, glucose phosphate, tartrate and acid tartrate.



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EUROPEAN SEARCH REPORT

Application Number
EP 97 12 0139

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	G. PROSDOCIMO ET AL.: "Miglioramento delle prestazioni funzionali dell' occhio senile dopo terapia con L-acetilcarnitina." BOLL. OCUL, vol. 70, no. 1, 1991, pages 57-62, XP002058277 & DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US accession no. 8544085, * abstract *	1-4	A61K31/22
X	G. PROSDOCIMO ET AL.: "Effetto della L-acetilcarnitina sulla soglia di sensibilità maculare in pazienti affetti da degenerazione maculare senile non essudativa." BOLL. OCUL., vol. 67, no. 4, 1988, pages 609-612, XP002058278 & DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US accession no. 6662184, * abstract *	1-4	<div>TECHNICAL FIELDS SEARCHED (Int.Cl.6)</div> <div>A61K</div>
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 9 March 1998	Examiner Klaver, T
<div>CATEGORY OF CITED DOCUMENTS</div> <div> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document </div>			

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